Physician and patient's adherence to antiretroviral prophylaxis after sexual exposure to HIV: results from south-eastern France AIDS IMPACT

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INTRODUCTION

Background

The efficacy of HIV prophylaxis in animal studies (Grob et al., 1997) and in prevention of vertical transmission (Wade et al., 1998) have resulted in the use of prophylaxis after sexual exposures to HIV in many developed countries (CDC, 2005; NSW, 1998; Rey et al., 2000). Different studies have shown that nPEP use does not increase the high risk behaviors (Martin et al., 2004). However, the lack of data about the usefulness of nPEP in patients at intermediate sexual risk and to what extent exposed cases adhere to medical follow up makes the results about the cost-effectiveness of nPEP difficult to interpret (Herida et al., 2006; Pinkerton et al., 2004).

The French context

Authorities produced in 1998 and in 2003 national detailed guidelines for nPEP (*Circulaires 228*, 1998 and *165*, 2003). Treatment is free of charge and available at every hospital. All people potentially exposed to HIV have to go within 48 hours to an emergency unit (EU) or an AIDS Care Unit (ACU) that are the only places where physicians are allowed to prescribe nPEP. Outside office hours, people can get a two days treatment (starter kit) at EU and then are referred to an ACU. If the continuation of nPEP treatment is decided by the AIDS care physician, guidelines recommend four-week combination antiretroviral therapy (cART) with medical and laboratory assessments at baseline and periodically for 4 months after exposure.

The present study formed part of the EURO-NONOPEP project supported by the European Commission (Almeda et al., 2004). This paper presents the results of a sub-survey carried out

in South Eastern France to characterize physician's adherence to guidelines and adherence to nPEP prescription in individuals sexually exposed to HIV.

MATERIAL AND METHODS

The survey was carried out in the 3 AIDS information centers (CISIH) which store the data of all individuals who have a consultation for nPEP in south eastern France. Retrospective data collection included information at the first visit after exposure and during follow-up for all individuals aged 15 years or more, who reported a sexual exposure between January 1st 2001 and December 31st 2002. Data collection included characteristics of exposed individuals and of the sexual exposure, delay between exposure and report, place of report, characteristics of the source person and nPEP prescription. Follow-up data included dates of visits, prescribed regimens, side-effects and interruption of treatment and biological results.

According to the French national guidelines, we built a three level variable to classify exposures into:

1. "High risk" exposures (treatment recommended): anal or vaginal unprotected intercourse with a HIV-positive partner, or a partner of unknown HIV-status belonging to a high risk group (injecting drug users or homo/bisexual men), or a partner of unknown HIV status in presence of aggravating factors
2. "Moderate risk" exposures (treatment on a case by case basis): other cases of anal or vaginal unprotected intercourse, or unprotected oral sex with a HIV-positive or unknown HIV-status partner belonging to a high risk group
3. "Negligible risk" exposures (treatment never recommended): other cases of oral sex or other sexual contacts

Due to missing information, evaluation of risk was not always possible.

NPEP and adherence to nPEP follow-up

Individuals receiving a 4 weeks cART prescription were invited to come back to the ACU at least once between the 2nd and 4th subsequent week for biological assessments. Cases followed up while receiving nPEP were considered as adherent to nPEP follow-up. Individuals missing this scheduled consultation at the ACU and those who received a 2 days starter kit and who did not come back to ACU to get the whole course of treatment were considered as non adherent to follow-up.

Statistical Analysis

Chi-squared tests and logistic models were used to identify factors associated with retention in nPEP treatment. A backward stepwise procedure based on the log likelihood ratio was used to identify the best set of significant predictors of the outcome in a multivariate model (entry threshold $p<0.20$). Statistical analyses were performed using the SPSS v 12.0.1 software program (SPSS, Inc., Chicago, IL, U.S.A.).

RESULTS

Number and characteristics of consultations

A total of 910 cases of sexual exposures were reported over the two years in South Eastern France, 457 in 2001 and 453 in 2002. In 69.3% of cases, first consultation took place less than 48 hours after exposure, and in 12.5% of cases, between 48 and 72 hours. Consultations mainly occurred at EU (61.7%). Nearly half cases reported that they came on their own initiative for a post-exposure consultation (n=422) and 149 were referred to hospital by a physician. The other cases were addressed by various sources including associations, police, sexually transmitted disease (STD) clinics, and friends.

The majority of the exposures (56.0%) were classified as “high risk”, 37.1% as “moderate risk”, 3.8% as “negligible risk” and the last 3.1% were unclassified because of lack of information. Sexual assaults were encountered in 108 cases.

Patients involved

Eight hundred and eighty four patients were exposed. Ten reported 2 different exposures and two, 3 different exposures. The majority of individuals were between 19 and 35 years (68.6%), 5.9% were 15-18 years, 21.4% were 36-50 years and 4.1% were more than 50 years. A majority (60.4%) were men, 39.2% were women and 0.3% were transsexuals. Among men, 220 reported a homosexual contact.

Prescription of a nPEP treatment

Treatment was prescribe in 87.9% of cases (n=800). The proportion of cases treated increased between 2001 and 2002 (85.3% versus 90.5% - p=0.017). Prescriptions were given for 93.3% of consultations occurring less than 48 hours after the exposure, 88.6% of those between 48 and 72 hours, and 66.7% of those after 72 hours. Cases whose consultations took place at EU were more likely to be prescribed nPEP than the others (92.9% versus 79.8%; p<0.001). Cases addressed by a physician were less likely to be prescribed nPEP than the others (80.59% versus 89.4%; p=0.003). None of the socio-demographic characteristics of individuals were associated with nPEP prescription. Cases reporting homosexual contacts did not receive nPEP more often than those reporting heterosexual contacts (90.9% versus 87.0% - p=0.117), but cases reporting ejaculation during exposure were significantly more prescribed than those not reporting it (90.4% versus 85.1% - p=0.013).

Physician's adherence to recommendations in case of sexual exposure was high: high risk and moderate risk exposures resulted in nPEP prescription in 92.5% and 85.0% of cases respectively, while 57.1% of negligible risk exposures also resulted in a prescription.

Among the 800 cases who were initially prescribed nPEP treatment, 24 refused including 11 who reported high risk exposures. The majority of the 776 cases who accepted (92.8%) were prescribed cART and the remaining 6.7% received a double combination therapy. The majority of prescriptions (85.3%) included a protease inhibitor.

Treatment follow-up after 1 month (n=776)

Among the 776 cases receiving nPEP, 26 individuals were followed up outside the region of the study, 1 individual discontinued his treatment before 48 hours as the source tested negative for HIV, 25 individuals discontinued nPEP after having taken the 48 hours starter kit following medical prescription and 197 did not come back after having been prescribed a starter kit for 48 hours, these latter mainly including consultations made at EU (67.2%). The 527 remaining individuals received a 4 week nPEP prescription. Among them, 90 did not come back and were lost to follow-up. Of the 437 remaining individuals who came back for consultation at the AC, 355 completed the treatment. Discontinuation of nPEP was recorded in 82 individuals: 28 stopped treatment as the source tested negative for HIV, 11 because of clinical side-effects, 2 because of biological side-effects (elevated transaminases and neutropenia), 11 for a personal choice, 3 cited other reasons and 27 were not documented.

Among the cases who received a one-month prescription and came back for consultation (n=437), 104 (23.8%) suffered from treatment-related side effects: nausea (10.8%), asthenia (5.7%), diarrhoea (5.3%), and vomiting (3.4%).

Characteristics of cases non adherent to nPEP medical follow up (n=287)

These 287 individuals included 197 who were lost to follow-up after receiving a 48 hours starter kit, and 90 who were lost after a 4 weeks prescription. Table 1 shows that independent characteristics associated with non adherence to nPEP follow up were younger age (<30), being referred to EU or ACU by a physician, sexual exposure with a casual partner or sexual assault, and "moderate risk" exposure.

Only one case (a 40 year old woman) was tested positive after having completed nPEP. She was consulted more than 72 hours after a high risk exposure.

DISCUSSION

South Eastern France is the main area concerned by the AIDS epidemic in metropolitan France after the Paris region (Lert et al., 2005). The evaluation of HIV-transmission risk enters prominently in the decision to prescribe, but more than half of the individuals with low-risk exposures were prescribed cART. Similarly, a large majority of consultations made more than 48 hours after sexual exposure resulted in a cART prescription. This "over-prescription" has already been observed in France and raises great concerns considering the non negligible risk of severe cART-related side effects (Laporte et al., 2002). Our data show that "overprescription" was more frequent in EU where the physicians are not AIDS specialists. With the daily difficulties encountered by physicians in overburdened EU, it is possible that a lack of time to fully evaluate each case's risk may have contributed to this "overprescription".

Poor adherence to medical follow-up in the context of HIV post exposure prophylaxis has already been widely documented but differences in reported rates of "lost to follow-up" greatly vary from one study to another (7% to 55%) (Day et al., 2006; Puro et al., 2004; Sonder et al., 2005). In our survey poor adherence to nPEP follow-up is particularly frequent among the youngest individuals and the victims of sexual assault. This result underlines the

need to inform and educate individuals on the importance of completing the whole course of nPEP including repeated serological control tests.

Among the 910 nPEP consultations, only one HIV seroconversion was reported. This seroconversion cannot be considered as a nPEP' failure as the delay between exposure and nPEP prescription was much higher than those recommended. The rate of HIV seroconversion in this study is much weaker than those described in other recent studies (Roland et al., 2005). Due to the limited duration of post-exposure follow-up, other HIV seroconversions may have occurred without being reported. This lack of follow-up represents the major difficulty in evaluating nPEP efficiency.

In our study, multiple consultations for the same person were extremely rare and mostly concerned condom breakage in serodiscordant couples. As with other studies (Kahn et al., 2001; Sonder et al., 2005) we can therefore confirm that nPEP is not used as a "morning-after- pill" and so does not lead to repetitive HIV related risky contacts.

Despite free of charge access, nPEP consultations for sexual exposures remain relatively infrequent when considering a population of 11 million adults in the surveyed area. This observation is consistent with results of French national surveys showing a lack of nPEP awareness (or of information about nPEP availability) in the general population (Beltzer and al, 2005) as well as in HIV-positive individuals (Rey et al., 2004) or in victims of sexual assault (Carrieri and al 2006).

In conclusion, despite the international debate on nPEP efficacy, the lack of a national register of nPEP prescriptions and the high rate of lost to follow up in the population sexually exposed to HIV receiving nPEP, French authorities have decided to give wide access to nPEP with the availability of starter kits in all EU throughout the country. Nonetheless, our findings highlight the need to implement new strategies and deliver concrete action guaranteeing a

better follow-up for individuals requiring a nPEP prescription. Those strategies have to include delivering proper information, creating a tracking process, and providing psychosocial support, particularly for the youngest patients and for survivors of sexual assault.

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Table 1 : Factors associated with non adherence to medical prescription (as expressed by retention in treatment) after nPEP prescription for sexual HIV exposure – univariate and multivariate analysis – n=776.

		Univariate analysis			Multivariate analysis		
	Total	Adherence to nPEP					
		Yes	No	p-value	AOR	95% CI	p-value
	776	**489 (63.0)**	**287 (37.0)**				
	(%)	**(%)**	**(%)**				
Age							
Less than 30 years	410 (52.8)	227 (55.4)	183 (44.6)	<10-3	1		<10-3
30 years or more	366 (47.2)	262 (71.6)	104 (28.4)		0.53	[0.39-0.72]	
Sexual classes							
Women	302 (38.9)	186 (61.6)	116 (38.4)	0.266			
Homosexual men	196 (25.3)	133 (67.9)	63 (32.1)				
Heterosexual men	278 (35.8)	170 (61.2)	108 (38.8)				
Referred to EU* or ACU by a physician**	659 (84.9)	428 (64.9)	231 (35.1)	0.008	1		0.005
No	117 (15.1)	61 (52.1)	56 (47.9)		1.81	[1.20-2.75]	
Yes							
Type of partner							
Steady partner	79 (10.2)	65 (82.3)	14 (17.7)	<10-3	1		0.001
Casual partner	599 (77.2)	371 (61.9)	228 (38.1)		2.29	[1.23-4.27]	
Sexual assault	98 (12.6)	53 (54.1)	45 (45.9)		3.88	[1.88-8.00]	
HIV sexual exposure***							
High risk	461 (59.4)	316 (68.5)	145 (31.5)		1		
Moderate risk	275 (35.4)	147 (53.5)	128 (46.5)	0.001	1.95	[1.39-2.75]	0.002
Negligible risk	20 (2.6)	12 (60.0)	8 (40.0)		1.44	[0.56-3.69]	
Not evaluated	20 (2.6)	14 (70.0)	6 (30.0)		0.97	[0.36-2.63]	
Type of sexual contact							
Heterosexual	580 (74.7)	356 (61.4)	224 (38.6)	0.104			
Homosexual	196 (25.3)	133 (67.9)	63 (32.1)				

* Emergency Unit
** Aids Care Unit
*** Only the evaluated risk is presented in the table, and not the variables entering into its construction.